

## The Investigation of Symptoms and Diagnoses of Adult-Attention Deficit/Hyperactivity Disorder in Women with Iron Deficiency Anemia

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### ABSTRACT

**Introduction:** The aim of this study was to investigate symptoms and diagnoses of Adult-Attention Deficit/Hyperactivity Disorder (ADHD) in women with iron deficiency anemia, to evaluate relationship between ADHD with clinical features and to compare with the women without iron deficiency anemia.

**Methods:** Eighty-three newly diagnosed iron deficiency anemia patients and 70 healthy controls were included in this study. All participants were assessed using a sociodemographic form, Structured Clinical Interview I (SCID-I), Wender Utah Rating Scale (WURS); Moreover, participants having WURS scores 36 and above were also assessed using the Adult ADD/ADHD Evaluation Scale and interviewed according to DSM-5 criteria.

**Results:** In the study, 22.9% of patients with iron deficiency anemia and 12.9% of healthy controls were found to have WURS scores 36 and above. Fifteen patients (18.1%) in iron deficiency anemia group

and two patients (2.9%) in control group had adult ADHD, when they were evaluated with Adult ADD/ADHD Evaluation Scale and interviewed according to DSM-5 criteria ( $p=0.007$ ). The patients with iron deficiency anemia had significantly higher WURS scores compared to controls ( $p=0.002$ ). The levels of iron and ferritin had negative correlation ( $r=-0.166$ ,  $p<0.05$ ;  $r=-0.255$ ,  $p<0.01$ , respectively) and the levels of serum iron binding capacity had positive correlation ( $r=0.255$ ,  $p<0.01$ ) with the scores of WURS.

**Conclusion:** The prevalence of adult ADHD is higher than those reported for general population in patients with iron deficiency anemia. Early diagnose and treatment of adult ADHD may positively contribute to the patients with iron deficiency anemia.

**Keywords:** Attention-deficit hyperactivity disorder, adult, iron deficiency, anemia

### INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is one of the most common childhood neuropsychiatric disorders, mainly characterized by hyperactivity, impulsivity and lack of attention. Recent studies suggest that this disorder is not limited to childhood but persists throughout the period of adulthood as well. ADHD is reported to affect the 5-10% of the school-age children across the world, 30-50% of whom have the same disorder as adults (1,2). On the other hand, adult ADHD prevalence was found 1-6% (3) whereas two recent meta-analyses reported this rate to be 2.5% (4) and 5.2% (5), respectively. The studies investigating the prevalence of adult ADHD in Turkey found the incidence rate to be 1.6% in outpatient psychiatric clinics (6), which ranged between 2.6% and 15.6% among the university students (7,8,9). Moreover, adult ADHD is demonstrated to be associated with reduced academic success, unemployment, frequent job switches, divorce and low socio-economic status (10,11,12).

The ADHD's pathophysiology remains unclear despite numerous studies investigating the etiology of the disease. Prenatal and perinatal risk factors, genetic factors and neurobiological alterations

are considered to be involved in its pathophysiology (13). Some studies have demonstrated that dopamine is the most important neurotransmitter included in ADHD's pathophysiology, regulating its main clinical features: psychomotor activity and executive functions (13,14).

The role of iron, a fundamental trace element, in ADHD's pathophysiology has been examined lately. It has been suggested that reduced cerebral iron increases ADHD risk notwithstanding any decrease in the peripheral iron levels of the body (15). The evidence for the role of iron deficiency and metabolism in the ADHD's pathophysiology includes the following: the cofactor role played by iron for the enzymes active in the synthesis and catabolism of monoaminergic neurotransmitters (16), the association between the reduced iron in the brain and the reduced density of receptors D2 and D4 as well as dopamine carriers (17), dysfunctional basal ganglions caused by iron deficiency (18), iron deficiency frequently displayed by children with attention deficit and hyperactivity accompanied by cognitive and behavior disorders (19), and demonstrated comorbidity of restless legs syndrome and the ADHD (20).



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Iron deficiency is the most common nutritional disorder across the world (21). Symptoms including weakness, irritability, communication disorders, reduced academic performance, regressed mental-motor development, reduced cognitive performance and papilledema are some of the effects caused by iron deficiency on the central nervous system. The iron level decreases in the central nervous system, and the iron-bound enzymes – required for the synthesis, activity and degradation of dopamin, serotonin and noradrenaline – deteriorate in the early stage of iron deficiency before it affects erythropoiesis. Deteriorated monoamine oxidase activity may result in reduced attention, memory and focus as well as apathy, sleepiness and irritability (22). Animal studies indicate that iron deficiency may cause structural and functional cerebral anomalies including altered dopamine metabolism, energy metabolism and myelination (23). Oades et al. have shown that cortical dopamine deficiency in rats results in hyperactivity and inhibition as well as impaired spatial orientation and temporal organization (24). Other animal studies further suggest that inadequate dopaminergic control in limbic striatal regions may hinder selective attention and behavioral inhibition (25,26). Results of in vivo studies imply that dopamine is likely to play a significant role in all the main symptoms of ADHD. Studies on humans suggest a significant relation between iron deficiency and low scores in tests evaluating infants' social and mental development, and it is also found related with reduced intelligence level, reduced learning and degraded neuropsychological functions (19). Recent studies claim that iron deficiency could be a risk factor for the ADHD (27,28,29).

Although there are studies in the literature investigating iron metabolism and deficiency in the ADHD, childhood ADHD in particular, there is no study examining the prevalence of ADHD among iron deficiency anemia patients according to our knowledge. This study aims to investigate adult ADHD prevalence among women diagnosed with iron deficiency, examine its relationship with clinical characteristics and compare them to those of women without iron deficiency.

## METHODS

### Participants

Research population consisted of the women diagnosed with iron deficiency anemia who referred to the Family Polyclinic of the Research Hospital of our university from May 1, 2014 to May 1, 2015, and who received no treatment (n=133), and healthy women with similar age and educational background (n=110). Serum ferritin level  $\leq 15$  ng/ml, considered the best non-invasive test in the diagnosis of iron deficiency, and hemoglobin level  $\leq 12$  g/dl were taken as points of reference (30). Volunteering, literate individuals within 18-50 age interval, without known mental disorder or deficiency, or organic and/or neurological disease that may harm cognitive functions, or regular medication, diagnosed with iron deficiency anemia and without other type of anemia or other diseases (patient group), and healthy individuals (control group) were included in the study. Patients and controls were assessed by the same psychiatrist with Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), and individuals with psychiatric diagnoses were excluded from the study. Of the patient group, 29 individuals were excluded based on exclusion criteria, 12 for refusing to participate in the study and 9 for providing incomplete information for the scales. On the other hand, 26 individuals from the control group were excluded based on exclusion criteria, 4 individuals refused to participate in the study and 10 individuals provided incomplete information for the scales. Thus 83 female patients comprised the iron deficiency anemia group and the control group included 70 healthy women.

### Procedure

Sociodemographic and laboratory details of the patients were recorded, and all participants were assessed using the Wender-Utah Rating Scale (WURS). Participants having WURS scores 36 and above (19 from the anemia group and 9 from the control group) were further assessed using the Adult ADD/ADHD Evaluation Scale and interviewed according to DSM-V criteria by the same psychiatrist. The study has been approved by the School of Medicine Clinical Research Ethics Board of our university and written consents of all participants have been obtained.

### Measures

**Sociodemographic Data Form:** This questionnaire has been developed by the researchers to determine the participants' sociodemographic characteristics for the purposes of this study.

**Wender-Utah Rating Scale (WURS):** It aims to assess the existence and severity of childhood ADHD symptoms and findings in adults, and originally contained 61 items. It was later reduced to the present version with 25 items sufficient to distinguish ADHD patients from the controls (31). It is a 5-point likert self-report scale with items ranging from 0 to 4 points. The scale has been translated into Turkish with demonstrated validity and reliability. Cut-off score was set for 36 (32).

**Adult ADD/ADHD Evaluation Scale (Turgay 1995):** Turgay's scale (33) is a 5-point likert self-report scale consisting of three sections. Section One contains nine questions formulated according to the DSM-IV diagnosis criteria, assessing the attention deficit. Section Two also relies on the DSM-IV criteria and includes nine questions that evaluate hyperactivity and impulsivity. Section Three consists of thirty items examining the characteristics that may be associated with the ADHD and other emotional and behavioral symptoms. At least six out of nine questions in both Section One and Two must be scored two or three for diagnosis. Section Three total score refers to the characteristics associated with ADD/ADHD. This scale is recommended for treatment and research as it is useful in distinguishing adult ADHD in the society at large and different clinical situations and offers high levels of validity, reliability and test-retest consistency (34).

**Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I):** This is a semi-structured interview schedule drafted to assess Axis I psychiatric disorder diagnoses in DSM-IV (35).

### Statistical Analysis

Statistical analyses were conducted using Statistical Package for Social Sciences (SPSS Inc.; Chicago, IL, USA) 15.0 software package. Variables were assessed for normal distribution using Kolmogorov-Smirnov test; normally distributed continuous variables were compared by t-test and others by Mann-Whitney U test. Chi-Square test was used for comparing categorical data. Relations among parametric numerical variables were analyzed with Pearson correlation test, and Spearman correlation test was used for analyzing non-parametric numerical variables.  $P < 0.05$  indicated statistical significance throughout the analyses.

## RESULTS

Individuals included in the study had a mean age of  $23.42 \pm 6.20$  and all participants were female. No statistically significant difference was observed between the groups in terms of age and educational background ( $p = 0.310$  and  $p = 0.860$ , respectively). The demographical and clinical characteristics of the iron deficiency anemia and control groups were

shown in Table 1. Iron deficiency anemia group displayed significantly higher WURS scores compared to the control group ( $p=0.002$ ). 22.9% of the iron deficiency anemia patients ( $n=19$ ) and 12.9% of the controls ( $n=9$ ) had WURS scores 36 and above. When individuals with WURS scores 36 and above are assessed according to the Adult ADD/ADHD Evaluation Scale and diagnostic interview based on DSM-V criteria, 15 (18.1%) patients with iron deficiency anemia and 2 (2.9%) individuals from the control group were diagnosed with ADHD. The difference was found statistically significant ( $\chi^2=9.79$ ,  $p=0.007$ ) (Table 2). 7 (46.6%) out of 15 patients with adult ADHD from the iron deficiency group were diagnosed with "predominantly inattentive type", 4 with "predominantly hyperactivity and impulsivity type" and 4 with "combined type". In the control group, 1 (50%) out of 2 patients with ADHD had "predominantly inattentive type" while 1 (50%) had "combined type". In terms of their Adult-ADD/ADHD Evaluation Scale scores, the iron deficiency group had significantly higher scores than the control group in the scores of attention deficit, hyperactivity and characteristics associated with ADD/ADHD ( $p<0.05$ ) (Table 3). As to the correlations between adult-ADHD scales and laboratory findings, there were negative significant correlations between WURS score and serum iron and ferritin level ( $r=-0.166$ ,  $p<0.05$ ,  $r=-0.255$ ,  $p<0.01$ , respectively), and a positive significant correlation with serum iron binding capacity ( $r=0.255$ ,  $p<0.01$ ). Moreover, a negative significant correlation was detected between serum iron level and ADD/ADHD scale hyperactivity score ( $r=-0.390$ ,  $p<0.05$ ). Table 4 shows the correlations between adult-ADHD scales and laboratory findings.

## DISCUSSION

Our study investigated the adult-ADHD diagnosis among patients with iron deficiency anemia, examined its relations with clinical characteristics and compared them to the results of the women without iron deficiency anemia based on the hypothesis that adult-ADHD diagnosis and

symptoms could be more prevalent among patients with iron deficiency anemia. Results have shown that adult-ADHD is more prevalent among the women with iron deficiency anemia compared to the healthy women, the former had higher adult-ADHD evaluation scores, and there were significant correlations between the laboratory findings of iron deficiency anemia and adult-ADHD evaluation scores. Our findings appear to confirm the hypothesis. To our knowledge, this represents the first study to investigate adult-ADHD symptoms, diagnosis and associated clinical characteristics in patients with iron deficiency anemia.

The studies conducted on adult-ADHD prevalence report it to fall within the interval of 1-6% (3,36). A Turkish study has found the prevalence of adult-ADHD to be 15.9% among the patients who referred to a general psychiatric polyclinic for the first time (37). Another study demonstrates adult-ADHD to be an important risk factor for lifelong psychiatric comorbidity (38). The exclusion of individuals with psychiatric comorbidities based on structured clinical interviews might be the reason for why the prevalence was found lower than it actually was in both iron deficiency anemia and control groups. In our study, 18.1% of the patients with iron deficiency anemia and 2.9% of healthy individuals were diagnosed with adult-ADHD. Such a high prevalence as 18.1% among the patients with iron deficiency anemia, which has not been reported before, indicates the importance of evaluating these individuals with respect to the adult-ADHD that may affect family relations, academic and business lives of these individuals. Furthermore, the ADHD prevalence among healthy controls were found to be in line with those reported before (4,36).

The predominant attention deficit type was the most commonly observed type of ADHD among the patients with adult-ADHD and iron deficiency anemia in our study. Clinical studies report the combined and predominantly inattentive ADHD types to be the most prevalent (39). In our country, of the two studies investigating ADHD among the patients referring to adult psychiatric clinics, one found predominant attention deficit type (37) to be more prevalent and the other reported combined type to be more frequently observed (6). Although our study features a limited number of patients with adult-ADHD in terms of the distribution of ADHD sub-types, the most prevalent ADHD types found in our study were the predominantly inattention and combined types, in line with the literature.

Iron, an essential trace element, plays a significant role for dopamine which is considered important for the ADHD's pathophysiology (28). Dopaminergic neurons and iron are found in the same cerebral regions (40). Iron was demonstrated to be found in high amounts in striatum, which plays a role in motor functions and behaviors (41,42) Since iron is a cofactor of tyrosine hydroxylase that is active in the dopamine synthesis, iron deficiency results in degraded dopamine synthesis and altered dopamine activity as well as receptor density. Moreover, iron is

**Table 1.** The demographical and clinical characteristics of the iron deficiency anemia and control groups (Mean  $\pm$  SD)

	Iron deficiency anemia (n=83)	Control (n=70)	p
Age	23.97 $\pm$ 6.60	22.77 $\pm$ 5.67	0.31
Education (year)	11.06 $\pm$ 2.79	10.97 $\pm$ 2.83	0.86
Hb	10.96 $\pm$ 1.03	13.56 $\pm$ 1.01	<0.001
Fe	31.16 $\pm$ 18.64	87.88 $\pm$ 43.46	<0.001
Ferritin	7.28 $\pm$ 3.23	33.29 $\pm$ 19.96	<0.001
Serum iron binding capacity	375.51 $\pm$ 50.72	269.64 $\pm$ 62.02	<0.001
WURS score	26.92 $\pm$ 15.15	20.62 $\pm$ 13.16	0.002

SD: Standard deviation; Hb: Hemoglobin; Fe: Iron; WURS: Wender-Utah Rating Scale

**Table 2.** The comparison between the groups according to adult ADHD diagnoses based on Wender-Utah Rating Scale cut-off score and clinical interview

		Iron deficiency anemia (n=83)	Control (n=70)	Total (n=153)	p
WURS score <36, n (%)		64 (77.1)	61 (87.1)	125 (81.7)	0.007
WURS score $\geq$ 36, n (%)	Patients with clinical diagnoses n (%)	15 (18.1)	2 (2.9)	17 (11.1)	
	Patients without clinical diagnoses n (%)	4 (4.8)	7 (10.0)	11 (7.2)	

ADHD: attention deficit/hyperactivity disorder; WURS: Wender-Utah Rating Scale

reported to be related with monoamine oxydase, which plays a role in dopamine catabolism (40,43). Furthermore, the variation of dopamine transporter gene is demonstrated to cause a genetic susceptibility to the ADHD (44). Reduced iron affects the function of iron-bound enzymes, degrading the synthesis and metabolism of dopamine, noradrenaline and serotonin (41,45). In our study, WURS and adult-ADHD Evaluation Scale (overall and subscales) scores used for measuring assessing the symptoms and findings of adult-ADHD were found significantly higher among the patients with iron deficiency anemia than the healthy individuals within the control group. This result demonstrates that patients with iron deficiency anemia had more severe adult-ADHD symptoms and is similar to those reported by studies revealing the relationship between iron deficiency and ADHD.

The studies investigating the relationship between ADHD and iron deficiency were conducted commonly on children with ADHD, and these studies reported contradictory results. The majority of studies employ ferritin as an indicator of iron deficiency. Ferritin is considered a reliable indicator of body iron stores. Some studies examining the relationship between serum ferritin levels and severity of ADHD symptoms have found a significant correlation (17,27,46,47,48,49,50) while others do not report such a relationship (15,43,51,52). As to the studies including control groups, two studies found significantly reduced ferritin levels in the ADHD group compared to the controls (27,51) while two others revealed no difference (43,52). Lahat et al. have demonstrated that re-

duced iron stores and iron levels play an important role in the ADHD's pathophysiology (13). Cortese et al. have reported that children with ADHD have significantly lower amounts of iron in right and left thalamus compared to the control group in their study examining iron levels in the putamen, globus pallidus, caudate nucleus and thalamus using magnetic resonance imaging (MRI) (15). In addition, there are studies showing the positive effects of iron treatments on attention and cognitive functions (53,54). That the WURS scores, used for assessing the severity of ADHD symptoms in our study, were found to be in significant negative correlation with serum iron and ferritin levels and in significant positive correlation with serum iron binding capacity supports other studies demonstrating the relationship between ADHD and iron deficiency. Moreover, the significant negative correlation between the hyperactivity score adult-ADHD Evaluation Scale and serum iron level can be seen as another finding that confirms our conclusion. The reason for the absence of a significant correlation with the scores in other sections of the Adult-ADD/ADHD Evaluation Scale might be that this scale was applied to the individuals scoring higher than WURS cutoff score only.

The strengths of our study can be listed as follows: participants without regular medication, inclusion of recently diagnosed patients with iron deficiency anemia, absence of physical comorbidities, similarities between groups in terms of age and educational background, absence of gender-related influences over the results since the population consisted of women only, exclusion of individuals with psychiatric comorbidities based on structured interviews, and diagnostic interviews conducted with individuals scoring higher than WURS cutoff score. The limitations of our study include the following: the study was designed as a cross-sectional one carried out with a limited sample in a single center, the prevalence was investigated for the female individuals only, and no information was received from the families or relatives of individuals as the patients were diagnosed with the ADHD. Despite such limitations, we consider our study to have contributed to the literature in researching adult-ADHD among patients with iron deficiency anemia for the first time.

The results of our study reveal that adult-ADHD diagnosis and symptoms are not rare among the patients with iron deficiency anemia. Given that symptoms of iron deficiency anemia include attention problems, presence of adult-ADHD diagnosis gains more significance. Early diagnosis and treatment of adult-ADHD could offer very positive benefits for patients with iron deficiency anemia.

**Table 3.** The comparison between the scores of Adult-ADD/ADHD Evaluation Scale of participants having WURS scores 36 and above in groups

	<b>Iron deficiency anemia (n=19)</b>	<b>Control (n=9)</b>	<b>p</b>
Adult-ADD/ADHD Evaluation Scale first section (Attention deficit) score	12.42 ± 6.00	8.00 ± 3.84	0.02
Adult-ADD/ADHD Evaluation Scale second section (hyperactivity) score	10.84 ± 5.83	6.00 ± 3.46	0.01
Adult-ADD/ADHD Evaluation Scale third section (The characteristics associated with ADD/ADHD) score	28.15 ± 18.95	16.88 ± 8.80	0.04
Adult-ADD/ADHD Evaluation Scale total score	52.52 ± 28.97	30.88 ± 13.86	0.02
WURS: Wender-Utah Rating Scale			

**Table 4.** The correlations between adult ADHD scales and laboratory findings

	<b>Age</b>	<b>Hb</b>	<b>Fe</b>	<b>Ferritin</b>	<b>Serum iron binding capacity</b>
WURS score	-0.007	-0.121	-0.166*	-0.255**	0.255**
Adult-ADD/ADHD Evaluation Scale first section (Attention deficit) score	0.096	-0.346	-0.057	-0.337	0.346
Adult-ADD/ADHD Evaluation Scale second section (hyperactivity) score	0.160	-0.293	-0.390*	-0.352	0.356
Adult-ADD/ADHD Evaluation Scale third section (The characteristics associated with ADD/ADHD) score	0.020	-0.124	-0.048	-0.250	0.314
Adult-ADD/ADHD Evaluation Scale total score	0.037	-0.252	-0.150	-0.329	0.353

ADHD: Attention deficit/hyperactivity disorder; WURS: Wender-Utah Rating Scale; Hb: Hemoglobin; Fe: Iron

\*p<0.05

\*\*p<0.01

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of local ethics committee.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - K.D., F.Y.B.; Design - K.D., F.Y.B., B.A., A.A.; Supervision - K.D., F.Y.B., A.A.; Resource - K.D., F.Y.B.; Materials - K.D., F.Y.B.; Data Collection and/or Processing - K.D., F.Y.B., B.A., Z.S., A.D.; Analysis and/or Interpretation - K.D., F.Y.B.; Literature Search - K.D.; Writing - K.D.; Critical Reviews - A.A., A.D.

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